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Office of Pesticide Programs
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This Position Document addresses the risks and benefits of pesticide products containing the subject active ingredient. The Agency has determined that the use of products containing the subject active ingredient may meet or exceed a risk criterion described in 40 CFR Part 154. Potential hazards will be examined further to determine the nature and extent of the risk, and considering the benefits of the subject active ingredient, whether such risks cause unreasonable adverse effects on the environment.

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EXECUTIVE SUMMARY

This Technical Support Document presents and describes the basis for the issuance of the Notice of Preliminary Determination proposing to cancel registrations and deny applications for registration for all pesticide products that contain cadmium compounds (salts of chloride, sebacate, succinate, carbonate and anilino cadmium dilactate) as active ingredients and that are for use on turf of golf courses and home lawns. The proposed action is based on the Environmental Protection Agency's (Agency) determination that the use of cadmium fungicides will result in unreasonable adverse effects to applicators of the products for these uses.

On October 26, 1977, the Agency issued a Notice of Rebuttable Presumption Against Registration (RPAR) and Continued Registration of Pesticide Products Containing Cadmium (42 FR 56574). The action was based on the Agency's finding that registrations of pesticide products containing cadmium met the then current 40 CFR 162.11(a)(3) risk criteria relating to oncogenicity, mutagenicity, teratogenicity, and fetotoxicity.

The Agency evaluated laboratory animal and human epidemiological studies and concluded that cadmium compounds are oncogenic and can cause kidney effects. The Agency also evaluated application exposure studies. In comparing the results of the toxicological studies with the estimated applicator exposures, the Agency concluded that there is up to a 10^{-4} lifetime risk of oncogenicity to certain applicators and low effect ratios for kidney effects.

The pesticidal usage of cadmium compounds is estimated to be approximately 30,000 pounds per year. This represents less than 0.1% of the total cadmium usage (30,000 to 35,000 tons) in the U.S. for industrial purposes. Although registered for use on both golf course and home lawn turf, cadmium fungicides are used almost exclusively by turf maintenance personnel on golf courses. The majority of this usage is concentrated in the region consisting of Minnesota, Wisconsin, Illinois, Indiana, Ohio and Michigan, where about 8% of the golf course acreage is treated with cadmium. In contrast, only about 2% of the total U.S. golf course acreage is treated with cadmium compounds.

The Agency reviewed information concerning the benefits relating to cadmium fungicide uses. The benefits were assessed relative to the economic impacts which would result if cadmium compounds were cancelled and users choose to use alternative fungicides. Agency estimates suggest that the annual impacts may be approximately $240,000 for the affected golf courses, or $500 per golf course using cadmium compounds, and negligible for the home lawn use.

The Agency also assessed the toxicological characteristics of the eleven registered alternative fungicides. The Agency concluded that for many of the alternatives, the risks associated with oncogenicity, mutagenicity, teratogenicity and reproductive effects are less than those for cadmium. For other alternatives the risks are of concern or are undefined due to the lack of essential data.

In weighing the risks and benefits and considering regulatory options, the Agency considered measures to sufficiently reduce applicator exposure and risk. The Agency evaluated the effectiveness and utility of these measures and concluded that they would not adequately mitigate exposure and risk.

In consideration of the toxicological effects of cadmium compounds, the estimated potential risks of these effects to applicators, the lack of effective measures to mitigate these unacceptable risks, the availability of effective alternatives and an estimated minor economic impact to users, the Agency has concluded that risks of continued use of cadmium pesticide products outweigh the minor benefits. Therefore, the Agency proposes to cancel all pesticidal uses of cadmium compounds.

I. INTRODUCTION

The Environmental Protection Agency (the Agency) is examining cadmium compounds because of oncogenic, mutagenic, teratogenic, fetotoxic, kidney, and male reproductive effects.

A. BACKGROUND

1. Regulatory History

The Federal Insecticide, Fungicide, and Rodenticide Act as amended (FIFRA) and its regulations require the Agency to review the risks and benefits of the uses of pesticides. On October 26, 1977, the Agency issued (42 FR 56524) a notice of Rebuttable Presumption Against Registration (RPAR) and Continued Registration of Pesticide Products Containing Cadmium. The Agency had determined that registrations and applications for registration of pesticide products containing cadmium met or exceeded the then current 40 CFR 162.11(a)(3) risk criteria relating to oncogenicity, mutagenicity, teratogenicity and fetotoxicity. The Notice also discussed other potential chronic metabolic effects.

The Notice invited comments from the registrants as well as from the public. Seven comments were received by the Agency. All substantive comments are addressed in this document.

2. Organization of this Position Document

This Technical Support Document (TSD) addresses the risks and benefits of the uses of cadmium pesticide products. It contains six parts. Chapter I is the introduction.

Chapter II discusses the potential risks of cadmium pesticide use including: descriptions and evaluations of the risk information, exposure data, rebuttal submissions and Agency analyses, and the Agency's risk conclusions. Chapter III discusses the benefits of cadmium pesticide uses on golf courses and home lawns, the assumptions and limits of these estimates, rebuttal submissions and Agency analyses, and the Agency's benefits conclusions. Chapter IV discusses the risks of the alternative pesticides to cadmium. Chapter V discusses the possible regulatory options to reduce the risks of cadmium pesticides, evaluates the risks and benefits of these regulatory options, and summarizes the regulatory actions which the Agency proposes to take concerning cadmium pesticides. Chapter VI is the bibliography.

3. The Special Review Process

The term "Special Review" is the name being used for the process previously called the Rebuttable Presumption Against Registration (RPAR) process (40 CFR 154).

The Special Review process provides a mechanism through which the Agency gathers risk and benefit information about pesticides, which appear to pose risks of adverse effects to human health or the environment that may be unreasonable. Through issuance of various Notices and support documents, the Agency publicly sets forth its position and invites the public and other Federal Agencies to participate in the Agency's review of suspect pesticides.

Risk evidence submitted to and/or gathered by the Agency must be evaluated and considered in light of the benefit information. If the Agency determines that the risks appear to outweigh the benefits, the Agency can initiate action under FIFRA to cancel, suspend, and/or require modification of the terms and conditions or regulations.

B. CHEMICAL BACKGROUND

1. Chemical and Physical Characteristics

Cadmium is a naturally occurring element, belongs to Group IIB in the periodic table of elements and has an atomic weight of 112.4. It constitutes 0.00001% of the earth's crust and is found primarily as the mineral Greenockite (cadmium sulfide), which is not mined commercially but is incidentally extracted during zinc and lead mining operations. Electrolysis of smelted ore yields 99.9% pure metallic cadmium. The melting point and boiling point of elemental cadmium are 321°C and 765°C, respectively; its density is 8.642 g/ml.

2. Registered Uses and Production

Pesticidal cadmium compounds are registered as fungicides for control of several turf fungus diseases on golf courses and home lawns. The compounds include the salts of chloride, sebacate, succinate, carbonate and anilino-cadmium dilactate. The latter two are not in current production but remain registered. The fungicides are available in a variety of formulations including, 1.5% - 20% soluble powders, 20% liquids, 8.5% and 60% wettable powder, and 0.8% granulars. Currently there are 23 registrants having 25 registrations. According to two major registrants (C.W. Cleary and Mallinckrodt Inc.),

cadmium fungicides are used exclusively for treatment of golf course turf.

Until 1968 cadmium compounds were registered both for use on turf and for limited use on food crops. Only one cadmium compound (anilino cadmium dilactate in mixture with phenylmercury formamide) was registered as a seed treatment for use on barley, flax, oats, rye, sorghum and wheat. Tolerances were established for these uses under the "no residue/zero tolerance" provisions of the regulations then in effect. After USDA, the federal agency responsible for pesticide regulation at that time, discontinued the application of the "no residue/zero tolerance" principle, all registrations for the use of cadmium on food crops were cancelled on February 1, 1968.

Industrial usage accounts for 99.9% of cadmium produced produced in the U.S. The industrial uses include pigment production, plastic stabilizers and nickel-cadmium battery production.

Many nonpesticidal uses of cadmium are subject to EPA regulations under the Safe Drinking Water Act (SDWA), Resource Conservation and Recovery Act (RCRA), Toxic Substance Control Act (TSCA) and the Clean Water Act (CWA). Cadmium is also subject to Occupational Safety and Health Administration (OSHA) regulations. EPA is preparing comprehensive technical regulations for the use/disposal of sewage sludge under Section 405(d) of the Clean Water Act. These regulations will establish criteria for application, distribution and marketing, landfilling, incineration and ocean disposal.

The current Agency primary drinking water standard for cadmium is 0.010 mg/L. The Agency in November 1985 published proposed regulations and draft Health Advisories for cadmium in drinking water. Final regulations and advisories are scheduled for publication in late 1986.

The Agency 's regulations for RCRA currently permit cadmium levels in sludge for landspreading on crop land. For example, the annual cadmium application rate (until December 31, 1986) is 1.25 kg/hectare. Beginning January 1, 1987, the annual cadmium application rates shall be 0.5 kg/hectare. Cumulative (multiple year) application rates shall not exceed 5 to 20 kg/hectare depending on soil pH and cation exchange capacity. These limitations are expected to change as EPA develops its Section 405(d) technical sludge regulations.

OSHA has published regulations (General Industrial Standards) for acceptable cadmium air concentrations (time weighted averages) based on oncogenicity: for an 8-hr day the values are 0.1 mg/m^3 and 0.2 mg/m^3 for cadmium fumes and dust, respectively; for a 15 min period the values are 0.3 mg/m^3 and 0.6 mg/m^3 for fumes and dust, respectively.

II. ASSESSMENT OF RISKS AND ANALYSIS OF PUBLIC COMMENTS

A. RISKS

The Agency concluded in the PD-1 that pesticide products containing cadmium met or exceeded the then applicable chronic and reproductive risk criterion relating to oncogenicity, mutagenicity, teratogenicity and fetotoxicity (40 CFR 162.11). The new criteria set forth at 40 CFR 154.7 would still be exceeded by these products.

1. Oncogenicity

a. Basis of Presumption

The Agency concludes that the use of cadmium pesticide products exceeds the chronic risk criteria relating to oncogenicity based upon (1) animal studies in which various cadmium compounds were administered orally and parenterally and (2) epidemiologic studies of humans exposed to cadmium by inhalation, dermal, and dietary (drinking water) routes.

In 1977 the Agency reviewed several laboratory and epidemiologic studies on the oncogenic properties of cadmium. It was concluded that (1) the number of tumors at sites removed from the site of injection increased significantly in animals injected with cadmium; (2) significant increases in prostate cancer were found in persons occupationally exposed to cadmium; and (3) chronic oral studies, although reported as negative by their authors, must be considered inconclusive because of protocol deficiencies. Some mutagenic actions of cadmium, including mammalian cellular transformations, have a high correlation with oncogencity. The epidemiological data alone indicated that

cadmium appears to be a potent carcinogen and provided evidence that the cancer criterion in 40 CFR 154.7 had been exceeded.

b. Analysis of Rebuttals Comments Concerning Oncogenicity

COMMENT

Mallinckrodt disagreed with EPA's determination that cadmium fungicides trigger the oncogenicity risk criteria. The company argued that: 1) because cadmium is a ubiquitous substance, epidemiological studies cannot provide a control group and should not be used support the oncogenic trigger, 2) EPA failed to consider animal evidence of the absence of an association between cadmium and prostate cancer, 3) the epidemiological studies EPA relied on for its oncogenic determination are not relevant to fungicidal use of cadmium as the exposure levels are significantly above those levels which humans might reasonably be anticipated to be exposed from the use of cadmium fungicides and 4) the two drinking water studies were not appropriate support of the Agency's oncogenic trigger, as the oral route of cadmium exposure was one that a pesticide applicator would not encounter.

RESPONSE —

The Agency considers Mallinckrodt's rebuttal arguments scientifically meritorious and has reconsidered its position that based on results of human epidemiological studies, exposure to cadmium pesticides is associated with increases in prostate cancer.

At the time of publication of the PD-1, the Agency considered all available data bearing on the potential oncogenicity of cadmium regardless of routes of exposure. It considered animal studies in which various cadmium compounds were administered orally and parenterally and epidemiologic studies of humans exposed to cadmium by inhalation, dermal, and dietary (drinking water) routes. It concluded that the results of the epidemiological studies alone indicated that cadmium pesticides posed an oncogenic risk and were sufficient to warrant a rebuttable presumption. Although the levels of cadmium exposure in the epidemiological studies were higher than would be encountered by pesticide applicators, the routes of exposure (dermal and inhalation) were the same. Also, the epidemiological studies were designed to distinguish whether or not there were differences in the incidence rates of tumors between control groups who were only exposed to background levels of cadmium, and factory workers who were exposed to additional levels of cadmium.

In 1985, EPA reviewed all the epidemiological studies and the two drinking water studies. It concluded that only four epidemiological studies (Potts, 1965; Kipling and Waterhouse, 1967; Lemen et at., 1976; and McMichael et al., 1976) provide evidence of a positive association of cadmium with prostate cancer. Due to protocol deficiencies in each, the evidence is now considered insufficient to conclude that cadmium is a prostate carcinogen. On the other hand, a dose-response lung cancer risk has been shown recently in both an epidemiological study (Thun et al., 1985) as well as a chronic rat inhalation study (Takenaka, et al., 1983).

After reviewing the two drinking water studies by Berg and Burbank (1972) and Zyka (1973), the Agency concluded that due to limitations in oral drinking water studies (i.e., sampling, age structure of population and unaccounted variables) no conclusions can be drawn about cadmium's relationship to cancer mortality from these studies.

c. New Information

In 1985, the Agency published an updated review and assessment of the literature on cadmium's oncogenicity and mutagenicity.

1. Animal studies

The Agency concluded that in rat and mouse studies, cadmium appears to be much more a potent carcinogen by inhalation and injection than by ingestion, regardless of the site of cancer induction.

In a chronic rat inhalation study by Takenaka et al (1983), male Wistar rats were exposed to cadmium chloride aerosol in concentrations of 12.5, 25, and 50 ug/m^3. Results showed a dose-related increase in the incidence of primary lung carcinomas in treated animals. Most carcinomas were detected after the 27th month of the study. It was also observed that cadmium was retained up to 13 months after cessation of exposure in the lungs, livers, and kidneys of surviving rats. In a pilot study by Heering et al. (1979), an increase in adenomas and adenocarcinomas was observed after 18 months of continuous exposure to cadmium chloride aerosol (20 ug/m^3).

In a rat acute inhalation study by Hadley et al. (1979), one lung tumor was reported among 34 male Wistar rats one year

after a single inhalation exposure of 60 ug/L of cadmium oxide for 30 minutes. Although the rats did not experience significant increases in lung tumors up to a year after dosing, they did develop a significant increase in numbers of mammary tumors and testicular degeneration. A significant increase in mammary tumors ($p=0.043$) was also observed in a study by Sanders and McHaffey (1984) where intratracheal instillations of 25 ug, 50 ug, and 75 ug of cadmium oxide were administered to male Fischer 344 rats. These results, along with the positive pulmonary findings in the Takenaka study, lead the Agency to conclude that cadmium oxide clears rapidly from the lungs and translocates into other tissues following inhalation, thereby presenting a hazard to both lung and extrapulmonary tissues.

Injection studies in mice and rats have been shown to produce sarcomas at the site of the injection as well as testicular and pancreatic islet tumors. In a rat study by Poirier et al., (1983), a significant increase ($p<0.02$) was observed in pancreatic islet cell tumors following subcutaneous injection of cadmium chloride over a two year period. Table II-1 taken from CAG's 1985 "Updated Mutagenicity and Carcinogenicity Assessment of Cadmium" summarizes the results of the injection studies reviewed.

In two chronic oral (drinking water) studies by Schroeder (1964 and 1965), doses of 5ppm of cadmium acetate were given to mice and rats. In both studies there was no statistically significant difference between the control group and treated rodents. Other chronic rat (Malcolm, 1972, Levy and Clark,

TABLE II-1

ANIMAL TUMORIGENESIS INDUCED BY CADMIUM INJECTION

Author	Species	Compound	Route	Tumor & Incidence
Haddow et al (1961)	Rats	Ferritin-containing cadmium	s.c.[a]	Sarcomas 8/20 Interstitial cell tumors 10/20
	Mice			Sarcomas 0/20
Heath (1962)	Hooded rats	Cd powder 0.28 g. in 0.4 ml fowl serum fowl serum	i.m.[b]	Sacromas 2/10 (later in study 10 more rats developed tumors; the test group they were in was not specified
Heath & Daniel (1964)	Hooded rats	Cd powder 0.014 g in 0.4 ml fowl serum	i.m.	Sarcomas 9/10
		0.028 g in 0.4 ml fowl serum		Sarcomas 6/8 (2 were killed early)
Kazantzis (1963)	Chester-Beatty rats	25 mg CdS in 0.25 ml physiological saline	s.c.	Sarcomas 6/10
Kazantzis and Hanbury (1966)	Wistar rats	25 mg CdS in 0.25 ml physiological saline	s.c.	Sarcomas 6/10, 6/26
		50 mg CdS in 0.50 ml physiological saline	i.m.	Sarcomas 5/14
		25 mg CdO in 0.25 ml physiological saline	s.c.	Sarcomas 8/10

[a]Subcutaneous
[b]Intramuscular

TABLE II-1 (cont)

Author	Species	Compound	Route	Tumor & Incidence
Haddow et al. (1964)	Rats	0.5 mg $CdSO_4.H^2O$ in 1.0 ml sterile distilled water once weekly for 10 weeks	s.c.	Sarcomas 14/20 controls 0/15
	Mice	0.05 mg $CdSO_4.H^2O$ in 0.2 ml H_2O once weekly for 11 weeks	s.c.	0/20 injection site tumors; controls 0/15
Malcolm (1972)	Rats	$CdCl_2$	s.c.	Sarcomas (?) Insterstitial cell tumors tumors (?) Experiment not completed at time of publication)
Levy et al. (1973)	C.B. Hooded Rats	0.2 mg $3CdSO_4.H^2O$ in 0.2 ml H_2O	weekly s.c. injection into alternate flanks for 2 years	Sarcomas 4/25 Interstitial cell tumors 17/5 1 lung adenoma
Malcolm (1972) (1972)	Rats	$CdCl_2$	s.c.	Sarcomas (?) Interstitial cell tumors (?) (experiment not completed at time of publication)
Levy et al. (1973)	C.B. Hooded Rats	0.2 mg $3CdSO_4.H^2O$ in 0.2 ml H_2O	weekly s.c. injection into alternate flanks for 2 years	Sarcomas 4/25 (1973) Interstitial cell tumors 17/25 1 lung adenoma
		0.1 mg $3CdSO_4.8H_2O$ in 2 ml 0.2 ml H_2O		Sarcomas 1/25 Interstitial cell tumors 17/25 1 malignant lymphoma

(cont.)

TABLE II-1 (cont)

Author	Species	Compound	Route	Tumor & Incidence
Levy et al (1973)	C.B. Hooded Rats	0.05 mg $3CdSO_4.8H_2O$ in 0.2 ml H_2O	weekly s.c. injection into alternate flanks for 2 yrs.	Sarcomas 1/25 Interstitial cell tumors 16/25 1 adenocarcinoma of pancreas
		controls - 0.2 mg H_2O only		Sarcomas 0/75 Interstitial cell tumors 48/75 1 squamous carcinoma of tongue 1 benign liver cell tumor
Scott and Aughey (1979)	Rats	0.5 ml injection into 1 mol $CdCl_2$ prostate		Prostate tumors 17/207
	Rats	0.5 ml 1 mol $CdCl_2$	s.c. five times	Negative for prostate
Poirier et al. (1983)	Wistar rats	7.3 mg/kg $CdCl_2$ in 0.9% NaCl	single s.c.	Sarcomas 14/50 Interstitial cell tumors 39/50
		3.6 mg/kg $CdCl_2$ in 0.9% NaCl		Sarcomas 12/50 Interstitial cell tumors 38/50
		controls - 0.9% NaCl		Sarcomas 0/50 Interstitial cell tumors 13/50

(cont.)

TABLE II-1 (cont)

Author	Species	Compound	Route	Tumor & Incidence
Roe et al (1964)	Rats	0.5 mg $CdSO_4$ in H_2O in 1.0 ml H_2O once weekly for 10 wks	s.c.	Interstitial cell tumors 11/15 Controls 0/15
		0.05 mg $CdSO_4.4H_2O$ in 02 ml H_2O		Interstitial cell tumors 0/16
Gunn et al (1963)	Albino mice	0.03 mM/kg $CdCL_2$	s.c.	Interstitial cell tumors 20/26 Controls 0/26
	Wistar rats	0.03 mM/kg $CdCl_2$	s.c.	Interstitial cell tumors 17/25 Controls 0/25
Gunn et al (1964)	Wistar rats	0.03 mM/kg $CdCl_2$	s.c.	Sarcomas 9/22 Interstitial cell tumors 0/18 Interstitial cell tumors 21/24; controls 0/18
Gunn et al (1967)	Wistar rats	1.8 mg $CdCl_2$	simultaneous s.c. and i.m.	Sarcomas 10/23 Sarcomas 3/26
Knorre (1970)	Wistar rats	0.003 mM $CdCl_2$/ 100 g b.w.	single s.c.	Sarcomas 6/45
Knorre (1971)	Wistar rats	0.003 mM $CdCl_2$/ 100 g b.w.	single s.c.	Interstitial cell tumors 10/25

(cont.)

TABLE II-1 (cont)

Author	Species	Cadmium Compound	Route	Tumor & Incidence
Lucis et al (1972)	Wistar rats	0.02-0.03 mM/kg $CdCl_2$ in isotonic NaCl solution	single s.c.	Interstitial cell tumors 13/15 Sarcomas 2/15 (two animals died early)
Reddy et al (1973)	Fischer 344 rats	0.03 mM/kg $CdCl_2$	single s.c.	Interstitial cell tumors 16/20 controls 0/10
Furst and Cassetta (1972)	Fischer 344	5 mg Cd powder (suspended in 0.2 ml synthetic trioctanoin)	2 monthly i.m.	Sarcomas 26/50
Favino et al (1968)	Sprague-Dawley rats	1 mg/100 g $CdCl_2$	single s.c.	Interstitial cell tumors 6/6

Data taken from U.S. Environmental Protection Agency. 1985 (June). Updated Mutagenicity and Carcinogenicity Assessment of Cadmium.

1975) and mouse (Levy et al., 1975) oral drinking water studies have shown no difference in tumor incidence between exposed and control groups. Although the studies indicate a lack of association between ingestion of cadmium and oncogenicity, the Agency believes that each study has protocol deficiencies (i.e., reduced survival times, limited histopathological examinations, deficient diets) which render them inconclusive for determinations of oncogencity.

2. Human epidemiological studies

When the Agency reviewed the many epidemiological studies of cancer in cadmium-exposed persons, they found that only four (Kipling and Waterhouse, 1967; Lemen et al., 1976; Holden, 1980; and Sorahan and Waterhouse, 1983) provide evidence of a statistically significant ($p<0.05$) positive association of cadmium with prostate cancer. Nevertheless, due to protocol deficiencies in each study, the results can only be considered suggestive. On the other hand, recent evidence of a significant dose-response lung cancer risk from exposure to cadmium is shown in the Thun et al. (1985) study.

In the Kipling and Waterhouse (1967) study, workers who had been exposed to cadmium oxide dust for a minimum of one year were shown to have an increase in prostate cancer ($p<0.003$). The results, although statistically significant, are weakened by the author's failure to allow a sufficient latency period. Futhermore, three of the four prostate cancer cases in this study were included in a study by Potts (1965) which was shown to contain selection bias. Therefore, the results of these studies cannot be considered independent of one another.

In 1976 Lemen et al. conducted a historical prospective study on male cadmium factory workers where air concentrations of cadmium dust measured in 1973 averaged below 1 mg/m^3. Statistically significant increases ($p<0.05$) were noted in prostate cancer and malignant respiratory diseases. After a lapse of twenty years from initial exposure, the finding of a statistically significant excess in prostate cancer was observed ($p<0.01$). Results of this study suggest an association of exposure to cadmium and prostate and broncogenic cancer. Nevertheless, the presence of arsenic in the atmosphere of the smelter and the possibility of increased smoking among the workers were potential confounding factors that contributed toward the significant association of broncogenic cancer and cadmium exposure.

In a study on British cadmium factory workers, (Holden, 1980) a statistically significant elevated risk of cancer was seen in the prostate ($p<0.01$) and the lung ($p<0.05$) of workers exposed to airborne cadmium in the plant as compared to workers in an iron and brass foundry. Nevertheless, due to the absence of a dose-response relationship between cadmium and prostate cancer and the presence of arsenic, silver and nickel fumes in the plant, the Agency believes that the association of exposure to cadmium and prostate and lung cancer can only be considered as suggestive.

In 1983 Sorahan and Waterhouse updated an earlier mortality study by Sorahan (1981) of workers in a nickel-cadmium battery factory. A subset of these workers (4) were also included in the Kipling and Waterhouse (1967) study. The authors prepared analyses with and without the original four cases included.

Results indicated an increased risk of prostate cancer ($p<0.05$) that was entirely dependent on the the four workers from the Kipling and Waterhouse study, but found no association with prostate cancer for cases other than these.

An increased risk of respiratory cancer was observed among workers moderately or highly exposed to cadmium oxide dust and initially employed before 1940, which was confounded by exposures to oxyacetylene welding fumes and to nickel hydroxide dust.

Several other studies reviewed by EPA suggest an increased risk of prostate cancer (although statistically nonsignificant) with exposure to cadmium (Potts, 1965; Kjellstrom et al., 1979; McMichael et al., 1967a, b; Anderssen et al., 1982; Kjellstrom, 1982; Varner, 1983 unpublished; and Thun et al. 1985).

When an updated version of the Lemen et al. (1976) study was done by Thun et al. (1985), the risk of prostate cancer was no longer statistically significant, while the risk of lung cancer remained. A nonsignificant risk of prostate cancer was observed in cadmium smelter workers, while a dose-related relationship was observed between lung cancer mortality and cumulative exposure to cadmium (levels in various parts of the plant ranging from 20 to 1,500 ug/m^3). The risk of lung cancer ($p<0.05$) was significantly in excess among workers hired both before and after the cessation of arsenic smelting activities in the plant. In order to minimize the significance of the confounding factors of arsenic exposure and cigarette smoking as contributors to the increased risk of lung cancer, the authors included average airborne arsenic exposures and worker's smoking habits in their calculations.

d. Conclusion

Based upon results of the studies in which (1) rats exposed to cadmium chloride aerosol by inhalation developed lung tumors, (2) rats and mice injected with cadmium or cadmium salts developed injection site, testicular and pancreatic islet tumors, and (3) workers exposed to airborne cadmium and cadmium compounds experienced a dose-related increase in lung tumors (Thun et al., 1985), the Agency classifies cadmium as a Group B1 substance and is considered to be a "probable" human carcinogen (Proposed Guidelines for Carcinogenic Risk Assessment, 1984).

2. Kidney and Other Adverse Effects

a. Discussion in PD-1

Cadmium has been shown to cause a number of health effects in humans who have been exposed for long periods of time to relatively high levels of cadmium (i.e., emphysema, proteinuria, liver dysfunction, hypertension, Itai-Itai disease, decreased hemoglobin levels, and vertigo). In addition, laboratory studies indicate that cadmium can cause a variety of adverse effects in experimental animals acutely exposed to cadmium by several routes of exposure (i.e., pulmonary edema, renal necrosis and temporary proteinuria, and liver dysfunction). Nevertheless, the Agency concluded that the frequency and duration of exposure necessary to produce these chronic effects in humans and the levels of cadmium necessary to produce acute human effects did not seem comparable to exposure from application of cadmium pesticides, taking into account ample margins of safety. Therefore, none of these effects was considered to warrant issuance of a presumption in the PD-1.

b. Rebuttal on cadmium's effects on the human metabolic systems

COMMENT

Mallinckrodt agreed with the Agency that, taking into account ample margins of safety, cadmium's effect on human metabolic systems did not warrant the issuance of a rebuttable presumption.

RESPONSE

Since publication of the PD-1 in 1977, the Agency has reviewed additional human and animal data on the adverse

effects of cadmium on the kidney and now believes the risk criteria at 154.7(a)(2) has been met. The basis for this decision is discussed below.

c. New Information

The effect of cadmium on kidneys has been studied in both experimental laboratory animals and occupationally exposed humans. Acute effects observed in experimental animals exposed to large amounts of cadmium include formation of fatty bodies and degeneration of renal tubules; chronic effects include proteinuria, glucosuria, excretion of amino acids in the urine and decreased renal function (NIOSH, 1976).

Absorbed cadmium is deposited in nearly all body tissues, with liver, kidneys, pancreas, and testes showing the highest levels (Probst, 1979). Cadmium deposits in the body reach a maximum at about age 50 and thereafter decline logarithmically. In the United States, the average concentration of cadmium (excluding occupational exposure) in the adult kidney at age 50 is 40 ug/g wet wt; the urinary excretion rate is less than 12 ug per liter (Friberg, 1974). Renal concentrations of cadmium are generally 5-100% higher in smokers than in non-smokers. A half-life for elimination has been estimated to be 10 to 33 years in humans and at least 200 days in animals (Ellis, et al., 1979). In humans, proteinuria may be the first sign of cadmium toxicity. B_2-microglobulin is the specific protein excreted in the urine. Exposure of 5-10 years may be required for this proteinuria to become evident (Friberg, 1950).

In 1979 South Carolina University conducted a study on golf course workers to measure cadmium and protein levels in urine.

The authors concluded that the measured levels were within normal ranges for the U.S. population. However, the results can only be considered as suggestive because of protocol deficiencies such as testing design, quality control in urine collection and subject selection criteria.

In a 1984 World Health Organization (WHO) study, an increase in renal tubular proteinurea and kidney tumors was seen in factory workers who were chronically exposed ($\leq$50 yrs) to cadmium oxide fumes and dust. A LOEL of 2 ug/m^3 was established from autopsies and biopsies of the workers. These effects were also seen in a 1950 human study (Friberg) in which long term cadmium exposure via inhalation was associated with proteinurea.

Recently, because of the demonstrated effect of cadmium on the kidney, the Agency conducted a quantitative assessment of the comparison of the demonstrated lowest observable effect level (LOEL) for kidney effects to the estimated exposures from registered uses. This assessment is more fully discussed in section II. D. These "Effect Ratios" (ERs) were calculated using the LOEL of 2 ug/m^3 from the Friberg, et al. (1974) and estimated application exposures (section II.B.4). The ERs ranged from 0.1 (dermal) and 4.0 (inhalation) for combined golf course applications to 88 (dermal) and 6666 (inhalation) for home lawn applications. Low ER values suggest a close association between exposure and the level shown to cause kidney effects; high values suggest less of an association.

d. Conclusion

Based on the results of: 1) animal studies where high doses of cadmium resulted in formation of fatty bodies and degeneration of renal tubules and human studies where chronic exposure to cadmium was associated with renal tubular proteinurea, the

Agency has concluded that the risk criteria of 40 CFR 154.7(a)(2) has been met.

3. Mutagenicity

a. Basis of Presumption

In 1977, the Agency concluded that the use of cadmium pesticide products exceeded the risk criteria relating to mutagenicity based on multitest evidence as required by the then current 40 CFR 162.11(a)(3) in which cadmium salts 1) increased the frequency of point and chromosomal mutations, (2) induced in vitro mammalian cellular transformation and, (3) enhanced transformation of virus-infected mammalian cells.

b. Analysis of Rebuttable Comments Concerning Mutagenicity

Comment

Mallinckrodt Inc. argues that EPA erred in its determination that cadmium fungicides trigger the mutagenicity risk criteria because the multitest evidence method is not a valid test method.

Response

In response to Mallinckrodt's rebuttal, the Agency no longer uses the "multitest evidence" protocol as the standard for FIFRA mutagenicity testing.

c. New Information

A review of all the existing studies on the mutagenic potential of cadmium in both prokaryotic and eukaryotic systems was done by the Agency in 1985. See Table II-2 for study results. It concluded that gene mutation studies in

TABLE II-2

MUTAGENICITY EVALUATION OF CADMIUM: GENE MUTATIONS IN PROKARYOTES

Test System	Strain	Cadmium Compound	Dose	S9 Activation System	Results	Comments	Reference
Salmonella typhiumrium	TA98 TA100 TA1535 TA1537 TA1538	CdCl in aqueous solution	0.05 0.5 5.0 50.0 500 ug/plate	Phenobarbital induced rat liver	Reported as negative	1. Data are not presented clearly as revertants/ plate for each strain. 2. Purity of compound not discussed	Heddle & Bruce (1977)
Salmonella typhiumrium	TA98 TA1535 TA1537	Cd red in DMSO	1 ug/ml	Aroclor 1254-induced	Reported as negative	1. Data provided only for the preincubation or suspension assay. No data on the spot test given 2. Only a single dose was employed; no dose-response data.	Milvy and Kay (1978)
Salmonella typhiumrium	TA1535 TA1537	CdCl (solvent-no specified)	10,20, 30, 45, 90 mM	Uninduced mouse liver	Reported as negative	1. Spotaneous reversion data and experimental reversion data have not been given in in terms of numbers. 2. Used uninduced mouse liver S9 activiation system 3. No positive controls	Polukhina et al (1977)

(cont.)

TABLE II-2 (cont.)

Test Systems	Strain	Compound	Dose	S9 Activation System	Results	Comments	Reference
Salmonella typhimurium	TA98 TA100 TA1535 TA1537 TA1538	Cd diethyl-thiocar-bamate in DMSO	1 5 10 100 ug/plate	Arochor-induced rat liver	Reported positive for TA1538 and TA98 in the absence of S9 acti-vation. Reported weakly + in both the presence and absence of S9 activation	1. Lowest effective dose was 10 ug/plate 2. Reported positive only for one dose 3. No dose-response relationship	Hedenstedt et al (1979)
Bacillus subtillis rec-assay	H17 Rec+ M45 Rec-	CdCl aqueous solution	0.05 M/plate	None	Reported as weakly (+) positive		Nishioka (1975)
		Cd nitrate aqueous solution			Reported as negative		
Bacillus subtillis rec-assay	H17 Rec+ M45 Rec-	Aqueous solutions of Cd chloride nitrite and sulfite	0.005 M/plate	None	Reported as weakly (+) positive	1. Compounds were pure	Kanematsu et al (1980)

Data taken from U.S. Environmental Protection Agency. 1985 (June). Updated Mutagenicity and Carcinogenicity Assessment of Cadmium

S. typhimurium (Heddle and Bruce, 1977; Milvy and Kay, 1978; Polukhina et al., 1977; and Hedenstedt et al., 1979), E. coli (Venitt and Levy, 1974), and yeast (Takahashi, 1972 and Putrament et al., 1977) produced inconclusive results.

Marginally positive responses were observed in gene mutation studies in mammalian cell cultures: mouse lymphoma cells (Amacher and Paillet, 1980 and Oberly et al., 1982) and Chinese hamster cells (Casto, 1976, Hsie et al., 1978, and Ochi and Ohsawa, 1983). See Table II-3 for study results.

In chromosomal aberration studies in human lymphocytes from exposed workers and human cell lines treated with cadmium, results were conflicting. Positive results were seen in two of the five in vivo studies. Results of seven in vitro studies show two positive, two weakly positive, and three negative. In studies where animals were treated with cadmium, chromosomal aberrations were observed in mouse carcinoma cells. No chromosomal aberrations or micronuclei were observed in the bone marrow of rodents treated with cadmium. Similarly, no dominant lethal mutations were observed in mice treated with cadmium. Existing evidence suggests that cadmium interferes with spindle formation both in vitro and in vivo studies in mammals. See Table II-4 for a listing of studies and results.

d. Conclusion

The Agency has reviewed many mutagenicity tests on cadmium compounds. The mutagenic potential of cadmium in producing gene mutations in both prokaryotic and eukaryotic systems is considered inconclusive, while marginally positive in mammalian cell cultures. Chromosomal aberration studies in humans provided

TABLE II-3

MUTAGENICITY EVALUATION OF CADMIUM: GENE MUTATIONS IN YEAST AND MAMMALIAN CELL CULTURES

Test System	Strain	Cadmium Compound	Dose	S9 Activation System	Results	Comments	Reference
Saccharomyces cerevisiae (yeast) P-mutants & auxotrophs	C3116	CdCl	10 12 20	none	Reported as positive	1. P-mutants may not represent true gene mutations because they arise by damage in mitochondrial DNA 2. Vague protocol	Takahashi (1972)
Saccharomyces cerevisiae P-mutants	197/2d	CdCl	8 ppm	none	Reported as negative	1. Only one concentration of test compound was used. 2. This concentration was too toxic for the cells. 3. No mutants observed in the few survivors	Putrament et al (1977)
Mouse lymphoma	L5178Y TK+/-	CdCl	0.05 0.06 0.08 0.11 0.15 ug/ml	none	Reported as weakly positive	1. Application of t-test to determine the significance has been challenged by Clive et al. (1981)	Amacher and Paillet (1980)

(cont.)

TABLE II-3 (Cont.)

Test System	Strain	Cadmium Compound	Dose	S9 Activation System	Results	Comments	Reference
Chinese hamster cells	Lung (don) cells; resistant to 8-azoguanine	Cd acetate CdCl	2.5 5 10 ug/ml	none	Reported as positive	1. Very low survival due to high toxicity 2. Observations not repeated or confirmed	Casto (1976)
Chinese hamster cells	Ovary cells (CHO)	CDCl	2.5 5 10 ug/ml	none	Reported as weakly positive	1. Data not presented	Hsie et al (1978)
Chinese hamster cells	V79	CdCl	$1x10^{-6}$M $2x10^{-6}$M $3x10^{-6}$M	none	Reported as positive		Ochie and Oshawa (1983)
Mouse lymphoma	L5178Y TK+/-	Cd sulfate	0.10 0.15 0.20 0.30 ug/ml	none	Reported as positive		Oberly et al (1982)

Data taken from U.S. Environmental Protection Agency. 1985 (June). Updated Mutagenicity and Carcinogenicity Assessment of Cadmium.

TABLE II-4

MUTAGENICITY EVALUATION OF CADMIUM: IN VIVO CHROMOSOMAL ABERRATIONS IN HUMANS

Species	Number of exposed Workers	Number of Controls	Duration of Exposure	Duration of culture (hrs)	Number of metaphases analyzed	Results	Comments	Reference
Human blood lymphocytes	14	5	3 mo - 26 yrs	48	2800 (exp) 900 (control)	Reported as negative	1. Sample size too small	Dekundt et al (1978)
Human blood lymphocytes	40	13	6 wks - 34 yrs	48	3740 (exp) 243 control	Reported as negative	1. Study was conducted following good cytogenetic procedure	O'Riordan et al (1978)
Human blood lymphocytes	7, 12	6, 9	not given	72	155/ person	Reported as positive	1. The history of the patients including exposure to other drugs was not given in these papers	Shiraishi and Yoshida (1972) Shiraishi (1975)

(cont.)

1.

TABLE II-4 (cont)

Species	Number of Exposed Workers	Number of Controls	Duration of Exposure	Duration of culture (hrs)	Number of metaphases analyzed	Results	Comments	Reference
Human blood lymphocytes from cadmium-exposed workers	5	3	5-24 yrs	48-72	100/ person	Reported as negative	1. Sample size too small	Bui et al (1975)
Itai-itai patients blood lymphocytes	4	4		72	100/ person	Reported as negative		
Human blood lymphocytes	24	15	3-6.5 yrs	48	4800 (exp) 1650 control	Reported as positive	1. The possibility of synergistic action of various metals cannot be ignored	Bachinger et al (1976)

Data taken from U.S. Environmental Protection Agency. 1985 (June). Updated Mutagenicity and Carcinogenicity Assessment of Cadmium.

conflicting results. Studies in animals have shown positive results in mouse carcinoma cells but negative results in rodent bone marrow. The existing evidence suggests conflicting results which cannot be readily resolved because of the many end points and protocols that have been used. Therefore, the Agency concludes that the weight of evidence from the composite of the many studies does not support the risk criteria for mutagenicity.

4. Teratology, Fetotoxicity, Reproduction

a. Basis of Presumption

The Agency concluded that the use of cadmium pesticide products met or exceeded the risk criteria relating to teratogenicity, fetotoxicity, and reproduction based on (1) animal studies where cadmium was seen to transfer across the placenta directly effecting the fetus as well as inducing maternal toxicity and (2) on the Agency's preliminary exposure estimates to women of childbearing age.

No comments were submitted to the Agency rebutting teratogenic, fetotoxic or reproductive risk concerns.

b. New Information

In 1985, the Agency reviewed animal and human teratology and fetotoxicity studies of cadmium. It concluded that: (1) cadmium is more readily absorbed through inhalation (10-40%) than through oral administration (1-5%), (2) in animal studies, less than 0.02% of a maternal dose crosses the placenta into the fetus, and (3) there is inadequate data to assess the effects of cadmium on human development.

In all treated animal species, cadmium was seen to be embryolethal, fetotoxic and teratogenic when administered parenterally. High doses resulted in fetal deaths whereas low doses caused fetal malformations/abnormalities.

In oral dosing studies, high doses were necessary to produce malformation of the fetus; otherwise, only reduction in fetal weights were observed.

In a female rat inhalation study, (Prigge, 1978), 0.04 to 0.12 ppm of cadmium administered 24 hrs/day throughout pregnancy caused reduction in maternal weight gains at all dose levels while only fetal body weight on day 21 of gestation was reduced significantly (19%) in a dose-related manner in the highest dose group. A NOEL of 0.6 mg/m^3 was determined for developmental effects.

Although there is some evidence that women living in highly industrial areas have higher blood and placental levels of cadmium than those in rural areas, there are inadequate data to assess the effects of cadmium on human fetal development. Tsvetkova, 1970, conducted a study of women factory workers from three cadmium producing factories; an alkaline battery factory where cadmium concentrations ranged from 0.1 to 25 mg/m^3, a chemical reagent factory where concentrations of soluble cadmium salts ranged from 0.16 to 35 mg/m^3, and a zinc molding factory where sulfoxide, sulfureous and metallic cadmium levels were 0.25 to 25 mg/m^3. All subjects were exposed to cadmium from 2 to 16 years. Results showed decreased birth weights for all exposed groups. Due to the small sample size and large variability in the three groups, the results can only be considered as suggestive.

Studies in rats, mice and hamsters have shown that very little cadmium (less than 0.02% of the maternal dose) crosses the placenta into the fetus. The amount of cadmium that crosses the placenta and localizes in the fetus is proportional to the

doses of cadmium administered to the maternal animal (Ishizu et al., 1973 and Chernoff, 1973). In a mouse study by Ishizu et al.(1973), cadmium was not found to be retained in fetal tissues 9 days after a single subcutaneous injection (5 mg/kg) on the 18th day of pregnancy, while high maternal levels were still found in the liver, kidney, and placenta. It was suggested by another researcher (Dencker, 1976) that in early pregnancy, cadmium more readily passes to a mouse embryo through the "Vitelline duct" but by the 8th day of pregnancy this duct closes and restricts the amount of cadmium passing into the embryo.

A number of human studies has shown the placental transfer of cadmium; however, the reported levels are variable and dependent on several factors (i.e., maternal age, diet, smoking habits). Flick et al., (1971) found cadium levels of 50 ug/kg in the human fetus, while earlier researchers using less sensitive methods had been unable to detect any cadmium in the fetus at term. Lauwerys, Buchet, Roels and Hubermont (1978) published a series of papers on cadmium levels in placenta, maternal and cord blood of Belgian women. Mean placental level of cadmium was 1.08 ug/100 g wet weight compared to a mean level of 0.10 ug/100 ml in maternal blood (Roels et al., 1978), suggesting the placenta concentrates cadmium about 10-fold. On the other hand, studies by Thurauf et al. (1975) and Baglan et al. (1974), reported mean levels of cadmium of 12.18 ug/100g in the placenta. Methodology differences may account for the disparity in results.

Similarly, there is sufficient evidence that cadmium may be passed to the infant through the breast milk, although transfer through breast milk is generally less than through the placenta. Murty and Thea, (1971) found a mean level of 0.027 ppm in breast milk from women living in an industrial area. Similarly, Schulte-Lobbert et al. (1978) found cadmium levels in breast milk ranging from 0.005 to 0.05 ppm, depending on maternal age and duration of lactation. The authors calculated that the weekly intake of cadmium in babies in the first month of life would average 0.04 mg, increasing to 0.12 mg by 8-12 months of age.

Studies in experimental animals have shown that when cadmium is introduced parenterally at high dosage levels, severe testicular damage is observed in both the tubules and interstitial cells (Probst, 1979). Intratesticular injection of cadmium has caused necrosis in all tested species (Chinquoine and Suntzeff, 1965). Results from an oral rat (drinking water) study indicated a dose of 68.8 ppm for 70 days yielded no significant reproductive toxicity (Zenick et al., 1982). No studies are available on the effects of cadmium on the testes using the inhalation route.

Studies in the literature have shown cadmium to accumulate in the ovaries of experimental animals after intravenous injection (Dencker, 1976 and Watanabe et al., 1977). Ovarian hemorrhage and follicular damage have been observed in subcutaneous injection studies (Parizek et al., 1968 and Kar et al., 1959). Prolonged estrous cycles were observed in a rat inhalation study by

Tsvetkova (1970) up to four months after cessation of cadmium doses of 3g/d for four months.

In occupationally exposed men, intermittent exposure to high levels of cadmium fumes resulted in decreased spermatids and spermatozoa (Smith, et al., 1960). However, due to many unaccounted environmental variables, the results are considered as only suggestive.

A study on nickel-cadmium factory workers was conducted by Favino et al. (1968). One exposed worker was seen to have a urinary testosterone level below average, while another exposed worker complained of impotence. Considering the flaws in the testing protocol (i.e., small number of test subjects, inadequate exposure histories, and variability in hormonal levels in control and exposed groups) it is not possible to draw any conclusions about the effects of cadmium on testicular and sexual function.

There have been no studies on the effects of cadmium on gonadal functions in women, except for the study of Tsvetkova (1970) showing no effect on the menstrual cycle.

c. Conclusions

Based upon the Agency's review of the animal studies, cadmium has been shown to produce developmental toxicity (embryotoxicity, fetotoxicity, and teratogenicity) in experimental animals. The effects shown appear to be dependent upon the dose and route of administration.

High parenteral doses of cadmium in male rats produce severe necrotic effects on the testes and generally irreversible infertility. Oral dosing is less effective due to the poor

absorption of cadmium from the oral route. The extent to which cadmium may exert its effects on the testes when administered by natural routes such as a pesticide applicator would encounter is still uncertain. In female rats, ovarian hemorrhage, follicular damage and estrous cycle changes have been observed only following doses of cadmium producing other signs of toxicity, but the effects appear to be transitory.

The available data are considered by the Agency as inadequate to support the risk criteria concerning teratogenic, fetotoxic and reproductive effects.

B. EXPOSURE

1. Environmental Exposure

Cadmium is present in the earth's crust at an average concentration of 0.18 ppm and is also a ubiquitous contaminant of air, water and soil. Emissions from industrial activities, trash burning, and dust from tread wear of car tires all contribute to the aerial load of cadmium.

Cadmium concentrations have been measured in different environmental substrates in the U.S. Reported concentrations range from 0.0006 to 0.12 mg/m^3 in air, from 0.01 to 0.17 ppm in drinking water, and from 0.89 to 1.27 ppm in soil. Concentrations appear to be related to the degree and type of industrialization of an area.

The greatest exposure to cadmium in the general populus is through dietary intake and smoking. Cadmium has been detected in foods of all categories monitored by FDA in its Market Basket Survey (1975). The highest amounts were found in leafy vegetables and canned foods (0.01 to 0.2 ppm). The high concentrations found in green plants result from translocation of cadmium from soil, which is fortified by small amounts of cadmium impurities contained in phosphate fertilizers and by unabsorbed cadmium ingested by animals and eliminated and redeposited in the soil or landfill (Schroder et al., 1963).

Cadmium is also found in cigarette smoke. The International Agency for Research on Cancer (IARC) reports that each cigarette contains 1.7 ug of cadmium, up to 10% of which can be absorbed through the lungs into the circulatory system.

In one year, moderate smoker (1 pack a day) may increase his/her total body burden of cadmium by 0.5 mg (IARC, 1976).

2. Pesticidal Exposure

Persons exposed to cadmium include golf course turf-maintenance personnel who apply cadmium fungicides to golf course greens, tees and fairways and homeowners and professional applicators from lawn care service companies who apply the fungicides to lawns. Inhalation and dermal exposure can occur during mixing, loading, and application.

Two application methods are used to treat golf course turf: (1) hand held spray guns for greens and tees and, (2) ground boom sprayers for fairways. Exposure is assumed to be greater for an applicator using a hand held spray gun due to the close proximity of the applicator's hands and legs to the cadmium emitted from the spray nozzle.

Cadmium is applied to golf course greens in both preventive and curative programs. Application rates vary depending on the type of program used. Of the four cadmium fungicides available, cadmium chloride and cadmium succinate have the greatest usage. For preventive programs cadmium succinate is routinely applied at 0.3 to 2.4 oz ai/1000 ft^2. Cadmium chloride is applied at 0.2 to 0.4 oz ai/1000 ft^2 for preventive programs and 0.4 to 0.5 oz ai/1000 ft^2 for curative programs. Typically the fungicides are applied about 12 times a year: in the spring and late summer and late fall to late winter seasons.

Several cadmium products are registered for home lawn use. Homeowners apply cadmium fungicides to their lawns with

garden sprayers or hose-end applicators. In contrast to golf course applicators, homeowners apply a significantly smaller amount of the fungicide (approximately 0.2 oz ai/1000 ft^2), fewer times a year (3 times) for a total treatment time of approximately 6 minutes/yr mixing and 180 minutes/yr applying.

3. Preliminary Applicator Exposure Assessment (1977)

At the time the PD-1 was published, the Agency was unaware of any definitive data indicating the precise quantities of cadmium to which humans were exposed as the result of the use of cadmium pesticides. In the absence of empirical evidence regarding human exposure, the Agency prepared a document entitled "Preliminary Analysis of Human Exposure to Cadmium from the Use of Cadmium Turf Fungicides."

Exposures were calculated for homeowners and golf course applicators for a single application of cadmium spray and dust formulations. The analysis provided estimates of inhalation and dermal exposure from typical cadmium fungicides applied as directed by the labels. Estimates for homeowners were based on dust and spray applications, while estimates for golf course applicators were based on spray application only.

For golf course applicators, total body dermal exposure from a spray formulation of 12% cadmium was estimated to be 80 mg. When using an absorption rate of 2% (Skog & Wahlberg 1964), and assuming that less than 1 pint of the liquid was in contact with the applicator's clothing, 1.6 mg of cadmium was calculated to be absorbed via the skin. The Agency estimated inhalation exposure

to be approximately two orders of magnitude less than dermal exposure (ca. 0.01 mg/m^3) based on the assumptions that (1) when the sprayer is held at waist height, only a fraction of the cadmium spray would enter the breathing zone and (2) because of the low volatility of cadmium, once the spray reached the turf it would not reenter the breathing zone of the applicator.

For a home lawn applicator the total body dermal exposure from a spray formulation of 3% cadmium was estimated to be 40 mg with 0.8 mg (2%) of cadmium being absorbed via the skin. For inhalation, the exposure was estimated to be 0.008 mg/m^3. When estimating exposures for dust formulations of 5% cadmium, the Agency assumed that (1) no applicator would come into contact with more dust than would cover all of his skin (at most 10 g of dust), (2) clothing would reduce dermal exposure by at least 90%, and (3) applicators would not tolerate large amounts of dust on exposed body parts for more than a few minutes. Based on the above assumptions the dermal exposure estimate was 0.5 mg. When estimating inhalation exposure for dust applications, it was assumed that the highest exposure would be during the loading of the spreader. Assuming 2 g/m^3 of dust would be within the applicator's breathing zone and using a breathing rate of 1.8 m^3/hr, in one minute an applicator would inhale 60 mg of the dust. With the dust containing 5% cadmium, the inhalation exposure would be 0.3 mg.

4. Rebuttal

COMMENT

Mallinckrodt argued that applicator exposure to cadmium from their products (Kromad and Cadminate) is insignificant.

They submitted a golf course study (Small and McGrath, 1978) in which applicators were exposed to their products by hand held spray gun applications to greens and tees. Inhalation and dermal exposures were measured. Inhalation exposure taken at the shirt collar level was reported to be 0.008 mg/m^3 (time weighted average). In determining dermal exposure, the authors measured the amount of cadmium that collected on the forearm of applicators wearing long sleeve shirts. The amount of cadmium measured was 2.84 mg with 0.05 mg being absorbed via the skin. Mallinckrodt points out that reported results for inhalation were well below the standards set by OSHA (200 ug/m^3) and recommended by NIOSH (40 ug/m^3 per 10 hr day) and dermal absorption is below the 1.6 mg of cadmium estimated by EPA as being absorbed.

RESPONSE

The Agency has reviewed the study by Small and McGrath (Golf Course Spray Operator Exposure to Cadmium Turf Fungicides) and concluded that it contains insufficient information for the Agency to determine worker dermal exposure to cadmium during hand spray applications on golf courses. Actual skin exposure was measured only to the forearms. Other body parts were not measured including the hands and legs which the Agency suspects would receive a large portion of the dermal exposure during downward-directed hand spray applications. The study does not indicate if mixing/ loading exposure is included and the number of replicates.

In regards to inhalation exposure, Small and McGrath reported air concentration of cadmium near the applicator's breathing zone was 8 ug/m^3 on a time weighted basis. Assuming a breathing volume of 1.74 m3/hr during light work, the respiratory exposure

is estimated to be 14 ug cadmium/hr. This compares favorably with the inhalation exposure of 43 ug cadmium/hr estimated from another pesticide exposure study (Daniels et al., 1980).

5. Applicator Exposure Assessment (1985)

An applicator exposure assessment was prepared by EPA (Lunchick, 1985) to determine golf course applicator and home lawn applicator exposure to cadmium fungicides. The Agency chose three studies to estimate golf course applicator exposure (one cadmium study and two surrogate studies) and one surrogate study to estimate home lawn applicator exposure. The range of application rates for cadmium succinate was determined by the Agency to be most representative of potential cadmium exposure for golf course applications. The application rates in Table II-5 were used in the Agency's exposure calculations. When using test data from the three golf course exposure studies, the Agency incorporated a conversion ratio to account for the differences between the EPA estimated application rates and the application rates used in the studies.

The Agency based its exposure calculations on an average body weight of 60 kg for estimated daily exposure and 70 kg for estimated yearly exposure (weights were based on the assumption that cadmium is a suspected oncogen and teratogen in women (60 kg) and a suspected oncogen in males (70 kg).

a. Golf Course Exposure Studies

The Agency used three studies to estimate golf course applicator exposure. In one study the registered product Cadminate was applied to greens and tees by a hand held spray gun (Daniel

TABLE II-5

APPLICATION RATES

Golf Courses and Homelawns

Site	Season	Application Rate (oz ai/1000 ft^2	Appl. per yr	Annual Hrs Mixing	Annual Hrs Applying
Greens and Tees	Spring-Late Summer	0.3	8	4.5	8
	Late Fall/ Late Winter	1.2 - 2.4	2	1.1	2
Fairways	Spring-Late Summer	0.3	3	2.1	24
Homelawns	"	0.2	3	0.1	3

Data provided in report of 28 Feb 1985, Use Practices and Potential Applicator Exposure Related to Cadmium Fungicides as Turf Grass Treatments, E.N. Pelletier (EPA)

et al., 1980). Due to the lack of exposure data from cadmium applied to fairways, two surrogate studies were used to estimate worker exposure when cadmium succinate is applied to fairways by ground boom spray. The two surrogate studies investigated exposure using a similar formulation during the mixing and loading and a similar application method during application. Everhart and Holt (1982) measured the potential exposure of mixer/loaders to the wettable powder benomyl, while Staiff et al. (1975) measured the exposure of workers applying paraquat by row boom spray.

In the first of the three studies used to estimate applicator exposure, Daniel, et al. (1980), applied a wettable powder formulation of cadmium succinate (Cadminate) at the rate of 0.15 oz ai/1000 ft^2 to golf course greens and tees by a hand held spray gun. The workers wore long sleeve shirts and pants during the mixing, loading and application. Patches in the clothed areas were placed under the clothing. Although Daniel did not measure exposure to the hands, the Agency assumes that hand exposure accounts for 90% of the total dermal exposure (Frankel, 1985). The workers did the mixing, loading and applying. Table II-6 presents the dermal exposure to cadmium determined by the study. The total dermal exposure to cadmium was estimated to be 0.82 mg/min. Air concentration of cadmium was 0.052 mg/m^3 during the 9 minutes of mixing and 0.021 mg/m^3 during the 64 minutes of application. The air concentration for combined activities was 0.025 mg/m^3 [(0.052 mg/m^3 x 9 minutes) + (0.021 mg/m^3 x 64 minutes) divided by 64 +9 minutes]. Assuming a respiratory volume for

TABLE II-6

EXPOSURE ASSESSMENT CALCULATIONS

Ground Application of Cadminate

Cadminate = 60% Cadmium Succinate = 29% Cd^{2+}
Application Rate = 0.5 oz Cadminate/1000ft^2
= 0.15 oz Cd^{2+}/1000 ft^2
Application Equipment = Hand held sprayer, pump set at 125 psi
Total Work Time = 243 minutes
Total Application/Mix Time = 90 minutes
Measured Application Rate = 0.46 oz/1000 ft^2

Hand Exposure Not Measured - Assumed to account for 90% of total dermal exposure

********** DERMAL **********

Sample	Concentration of Cd (ug/100cm^2)	Body Surface Area (cm^2)	Body Surface Area/Pad Area	Dermal Exp. (ug)
Front		Chest and stomach=	3550/200 =	
Upper Body	15.4	3550	17.75	273
Lower Body	13.5	"		240
Back		Back = 3550	3550/200 =	
Upper Body	13.5	"	17.75	240
Lower Body	25.0	"		444
Right Ankle	8.0	Lower Leg= 1190	11.9	95
Left Ankle	11.0	"	11.9	131
Right Wrist	516.0	Forearm = 605	6.05	3122
Left Wrist	467.0	"	6.05	2825

Dermal Exposure = 7370 ug
Dermal Exposure Rate[1] = 7370 ug/90 min = 82 ug/min
Total Dermal Exposure Rate[2] = 82 ug/min/0.10 = 820 ug/min

[1] Actual time spent mixing and applying fungicide
[2] Includes assumed exposure to hands

light work of 1.7 m^3/hr, the respiratory exposure to cadmium is 0.043 mg/hr (0.025 mg/m^3 x 1.7 m^3/hr) for hand spray application to greens and tees.

Using a conversion ratio of 2 (to adjust for the difference between EPA's estimated application rate of 0.3 oz ai/1000ft^2 and Daniel's application rate of 0.15 oz ai/1000 ft^2) the estimated exposure rates (summer) for golf course applicators using hand held spray guns are as follows:

Daily dermal exposure = 2.6 mg/kg/day

0.82 mg/min x 60 min/hr x 2.0 x 12.5 hr/yr
divided by 8 days/yr divided
by 60 kg = 2.6 mg/kg/day

Daily respiratory exposure = 0.002 mg/kg/day

0.043 mg/hr x 2.0 x 12.5 hrs/yr
divided by 8 days/yr divided by 60 kg = 0.002 mg/kg/day

Annual dermal exposure = 18 mg/kg/day

0.82 mg/min x 60 min/hr x 2.0 x 12.5 hr/yr
divided by 70 kg = 18 mg/kg/yr

Annual respiratory exposure = 0.015 mg/kg/yr

0.043 mg/hr x 2.0 x 12.5 hrs/yr
divided by 70 kg = 0.015 mg/kg/yr

Using a conversion ratio of 16, (to adjust for the difference between EPA's tested application rate of 2.4 oz ai/1000ft^2 and Daniel's application rate of 0.15 oz ai/1000ft^2) the estimated exposure rates (late fall/late winter) for golf course applicators using hand held spray guns are as follows:

Daily dermal exposure = 20.3 mg/kg/day

0.82 mg/min x 60 min/hr x 16 x 3.1 hr/yr
divided by 2 days/yr divided by 60 kg = 20.3 mg/kg/day

Daily respiratory exposure = 0.018 mg/kg/day

0.043 mg/hr x 16 x 3.1 hr/yr
divided by 2 days/yr divided by 60 kg = 0.018 mg/kg/day

Annual dermal exposure = 34.9 mg/kg/yr

0.82 mg/min x 60 min/hr x 16 x 3.1 hr/yr
divided by 70 kg = 34.9 mg/kg/yr

Annual respiratory exposure = 0.03 mg/kg/yr

0.043 mg/hr x 16 x 3.1 hr/yr
divided by 70 kg = 0.030 mg/kg/yr

Two surrogate studies were used to estimate worker exposure when cadmium succinate was applied to golf course fairways by ground boom spray. Everhart and Holt (1982) measured the potential exposure of mixer/loaders to the wettable powder benoyml. During the study 10 mixer/loaders added benomyl powder to mixing tanks containing water. The benomyl was 50% active ingredient. Dermal exposure was measured by attaching gauze pads to the shoulders, chest, back and forearms to either exposed skin or the outer garments. Hand exposure was measured using cotton gloves. Filter pads attached to a respirator were used to measure respiratory exposure. Back and chest exposures determined by the author were reduced by 80% to adjust for clothing. The exposure was:

Area	mg/m^2	mg/body area	adjusted mg/body area
Forearms	75	9.1	9.1
Face	27	1.7	1.7
Back of neck	9	0.10	0.10
Back	9	3.2	0.64
Front of neck	15	0.23	0.23
Chest	15	5.4	1.1
Hands	150	12	12

TOTAL Dermal = 25 mg
" " Respiratory = 0.08 mg

The mixer/loaders handled an average of 208 lbs ai over an average of 3.14 minutes. The exposure to mixer/loaders was 0.12 mg/lb ai for dermal and 3.8×10^{-4} mg/lb ai for inhalation.

To estimate applicator exposure on golf course fairways, the Agency has made the assumption that a typical golf course has 40 acres of fairways. Using EPA's estimated application rate of 0.3 oz ai/1000 ft^2, a total of 9.5 lbs cadmium is handled per application. Incorporating data from the Everhart and Holt study, the estimated exposures for mixers/loaders applying cadmium succinate to fairways are as follows:

Daily dermal exposure = 0.019 mg/kg/day

0.12 mg/lb ai x 9.5 lbs ai/day
divided by 60 kg = 0.019 mg/kg/day

Daily respiratory exposure = 0.00006 mg/kg/day

3.8×10^{-4} mg/lb ai x 9.5 lbs ai/day
divided by 60 kg = 6.0×10^{-5} mg/kg/day

Annual dermal exposure = 0.049 mg/kg/yr

0.12 mg/lb ai x 9.5 lbs ai/day x 3 days/yr
divided by 70 kg = 0.049 mg/kg/yr

Annual respiratory exposure = 0.00015 mg/kg/yr

3.8×10^{-4} mg/kg/lb ai x 9.5 lbs ai/day x 3 days/yr
divided by 70 kg = 1.5×10^{-4} mg/kg/yr

The second surrogate study by Staiff, et al., (1975) measured the exposure of workers applying paraquat by row boom spray at an application rate of 1.0 lb ai/A. Applicator dermal exposure was calculated at 0.40 mg/hr based on the workers wearing short sleeve shirts and long pants. Respiratory exposure was measured by attaching filter pads to respirators and was estimated at less than 0.001 mg/hr.

When estimating ground boom applicator exposure using the exposure data from the Staiff study, a conversion ratio of 0.81 was used to adjust for the difference between EPA's application rate of 0.3 oz ai/1000 ft^2 and Staiff's rate of 0.37 oz ai/1000 ft^2. The exposure estimates for ground boom applicators are as follows:

Daily dermal exposure = 0.043 mg/kg/day

0.40 mg/hr x 0.81 x 24 hr/yr
divided by 3 days/yr divided by 60 kg = 0.043 mg/kg/day

Daily respiratory exposure = 0.00011 mg/kg/day

0.001 mg/hr x 0.81 x 24 hr/yr
divided by 3 days/yr divided by 60 kg = 1.1×10^{-4} mg/kg/day

Annual dermal exposure = 0.11 mg/kg/yr

0.40 mg/hr x 0.81 x 24 hr/d
divided by 70 kg = 0.11 mg/kg/yr

Annual respiratory exposure = 0.00028 mg/kg/yr

0.001 mg/kg/hr x 0.81 x 24 hr/yr
divided by 70 kg = 2.8×10^{-4} mg/kg/yr

The Agency expects that one individual would perform the mixing, loading and application of cadmium succinate to fairways. Therefore the mixer/loader exposures from the Everhart and Holt study and the applicator exposure studies from the Staiff study can be used to give exposure estimates for mixing, loading and applying cadmium succinate to fairways by ground boom. The combined exposures are as follows:

Daily dermal exposure = 0.062 mg/kg/day

0.019 m/kg/day + 0.043 mg/kg/day = 0.062 mg/kg/day

Daily respiratory exposure = 0.00017 mg/kg/day

6.0×10^{-5} mg/kg/day + 1.1×10^{-4} mg/kg/day
= 1.7×10^{-4} mg/kg/day

Annual dermal exposure = 0.16 mg/kg yr

0.049 mg/kg/day + 0.11 mg/kg/day = 0.16 mg/kg/yr

Annual respiratory exposure = 0.00043 mg/kg/yr

1.5×10^{-4} mg/kg/yr + 2.8×10^{-4} mg/kg/day = 4.3×10^{-4} mg/kg/yr

The daily cadmium exposure to an individual treating golf course greens, tees, or fairways is estimated to range from 0.062 to 20 mg/kg/day by the dermal route and from 1.7×10^{-4} to 0.018 mg/kg/day by inhalation, depending on the application rate and method of application.

The annual cadmium exposure to an individual conducting all applications to golf course greens, tees, and fairways is estimated to be 53 mg/kg/yr by the dermal route and 0.045 mg/kg/yr by inhalation.

b. Home Lawn Use Exposure Study

A surrogate study by Davis et al. (1983) was chosen to estimate cadmium exposure during home lawn application. In the surrogate study diazinon liquid was applied by hose-end sprayer at an application rate of 70 g ai/1000 ft^2. Alpha-cellulose pads were attached to the skin on the shoulders, back, chest, forearms, thighs, and ankles to measure dermal exposure. Hand exposures were measured by hand rinses. Respiratory exposure was measured by respirator filter pads. One set of applicators wore bathing suits and shoes and a second set wore short sleeve shirts, long pants, and shoes. The exposure data are presented in Table II-7. Based on the Davis study, the use of liquid cadmium chloride for home use would expose the home user to a dermal exposure of 2.0 mg/hr and a respiratory exposure of

TABLE II-7

EXPOSURE ASSESSMENT CALCULATIONS

A. Actual Exposure Assessment Study - Home Lawn Application of Diazinon

Diazinon (liquid) = 25% active ingredient, 57% aromatic petroleum derivative solvent, 18% inert ingredients
Application rate = 5 oz/15 gal 15gal/500 ft^2
Application equipment - garden hose-end sprayer
Application/mix time = 30 minutes
Amount of Spray used = 30 gal (1000ft^2)

********** DIAZINON EXPOSURE (ug/hr) **********

		Minimal Clothing[1]		Normal Clothing[2]	
Respiratory	Hands	Dermal(w/o hands)	Total	Dermal(w/o hands)	Total
7.4	25000	4100	29000	540	25000

B. Surrogate Exposure Assessment - Home Lawn Application of Caddy

Caddy = 20.1% cadmium chloride = 12.3% cd^{2+}
Application Rate = 1.6 oz Caddy/1000 ft^2
= 514 g Cd^{2+}/1000 ft^2
Cd: Diazinon Conversion Ratio = 5.4 g Cd^{2+}/1000 ft^2 divided by 70 g diazinon/1000ft^2 = 0.08

********** CADMIUM EXPOSURE (ug/hr) **********

		Minimal Clothing[1]		Normal Clothing[2]	
Respiratory	Hands	Dermal(w/o hands)	Total	Dermal (w/o hands)	Total
0.6	2000	330	2300	43	2000

[1]Bathing suit and shoes
[2]Short-sleeved shirt, long pants, and shoes

0.0006 mg/hr, assuming home users wear short sleeve shirts, long pants, and shoes during application.

The estimated exposure to cadmium during home use is as follows:

Daily dermal exposure = 0.035 mg/kg/day

2.0 mg/hr x 186 min/yr divided by 60 min/hr divided by 3 days/yr divided by 60 kg = 0.035 mg/kg/day

Daily respiratory exposure = 0.00001 mg/kg/day

0.0006 mg/kg/hr x 186 min/yr divided by 60 min/hr divided by 3 days/yr divided by 60 kg = 1.0×10^{-5} mg/kg/day

Annual dermal exposure = 0.089 mg/kg/yr

2.0 mg/hr x 186 min/yr divided by 60 min/hr divided by 70 kg = 0.089 mg/kg/yr

Annual respiratory exposure = 0.000027 mg/kg/yr

0.0006 mg/hr x 186 min/yr divided by 60 min/hr divided by 70 kg = 2.7×10^{-5} mg/kg/yr

6. Dermal Exposure Estimate with Protective Gloves and Respirators

The Agency considered as one of its regulatory options to require the use of protective clothing to be worn during the mixing, loading and hand held spray application of cadmium products for golf course use and home lawn use.

The Agency re-calculated the exposure data from the Daniel et al. study (Table II-6) to estimate worker exposure when applying cadmium to greens and tees with protective gloves. The exposure assumptions and usage data remain the same except that the exposure received by the wrists also represents hand exposure and the Agency assumes from the results of the Daniel et al. study that elbow length gloves reduce wrist and hand exposure by 90%. Based on the use of

protective gloves, wrist exposure decreases from 3122 to 312 (right) and from 2825 to 283 (left). Dermal hand exposure is estimated to be 212 (right) and 191 (left). Based on these revised calculations, the use of protective elbow length gloves during mixing/loading and application will reduce dermal exposure to 27 ug/min. The daily and annual dermal exposures for hand spray application to greens and tees would be 84 ug/kg/day and 580 ug/kg/yr. respectively. With the proper use of half-face respirators, inhalation exposure would be reduced by one order of magnitude.

For the home lawn use, the Agency considered whether or not the use of gloves and respirators would be practical and effective in reducing exposure. While the use of chemical resistant gloves and a half face respirator would be expected to reduce exposure for the home lawn application as well, the Agency does not believe such use requirements would likely and consistently be followed by the home owner. Therefore, a detailed analysis of potential exposure reduction is not presented.

C. RISK ASSESSMENT FOR ONCOGENICITY

The Agency has prepared a risk assessment of the oncogenic risks of persons applying cadmium fungicides to golf courses and home lawns based on inhalation exposure estimates. Only inhalation exposure, rather than inhalation and dermal exposures, was considered as pertinent because the Agency has concluded (see Section II.A.1 -Oncogenicity) that the data base only support the formation of lung tumors following inhalation exposure to laboratory animals and smelter workers.

Cancer potency was developed based on respiratory cancer rates from the Thun et al. (1985) study of cadmium smelter workers. Using a linear model consistent with the data, the upper-bound incremental cancer risk from lifetime exposure (time weighted average) to 1 ug/m^3 of cadmium in the air is estimated to be 1.8×10^{-3} $(ug/m^3)^{-1}$. A higher estimate of 3.5×10^{-3} $(ug/m^3)^{-1}$ would be obtained if the 95% upper bound of the parameter were used. However, the Agency feels that this is an unnecessary added level of conservatism since the model being used already inflates the risk estimate if nonlinear components exist or confounding factors are present.

The Agency considered using the Takenaka et al. (1983) rat inhalation study for a potency determination. Data from this study gives a higher estimate: 9.2×10^{-2} $(ug/m^3)^{-1}$. However, species differences and cadmium form (aerosol) differences make an estimate from the animal data less reliable than the one derived from the Thun et al. (1985) study of cadmium production

workers (i.e., pesticidal applicators are not exposed to cadmium aerosol particles which are more readily absorbed than fumes). Although there is uncertainty in the human risk estimate due to differential exposure in the workplace, the Thun et al. study is regarded as more realistic than the estimate based on the rat inhalation study for the reasons outlined above.

The exposure estimates used in the risk assessment are from the Agency's Exposure Assessment presented in section B of this chapter. The inhalation exposure was adjusted for Lifetime Average Daily Dose (LADD) assuming that cadmium is applied 35 years of a 70 year lifetime. The LADD is calculated as follows:

$$\text{LADD} = \text{mg/kg/yr} \times \frac{35 \text{ yrs.}}{70 \text{ yrs.}} \times \frac{1 \text{ year}}{365 \text{ days}}$$

The LADD inhalation exposure estimates for golf courses using cadmium succinate and homeowners using cadmium chloride are as follows:

1. Golf Courses

Hand held spray gun (tees and greens)

Summer = 2×10^{-5}

$$0.015 \text{ mg/kg/yr} \times \frac{35 \text{ yrs}}{70 \text{ yrs}} \times \frac{1 \text{ yr}}{365 \text{ days}} = 2 \times 10^{-5} \text{ mg/kg/d}$$

Late Fall & Winter = 4×10^{-5}

$$0.030 \text{ mg/kg/yr} \times \frac{35 \text{ yrs}}{70 \text{ yrs}} \times \frac{1 \text{ yr}}{365 \text{ days}} = 4 \times 10^{-5} \text{ mg/kg/d}$$

Mixer/loaders (fairways) = 2×10^{-7} mg/kg/day

$$1.5 \times 10^{-4} \text{ mg/kg/yr} \times \frac{35 \text{ yrs}}{70 \text{ yrs}} \times \frac{1 \text{ yr}}{365 \text{ days}} = 2 \times 10^{-7} \text{ mg/kg d}$$

Ground Boom (fairways) = 4×10^{-7} mg/kg/day

$$2.8 \times 10^{-4} \text{ mg/kg/yr} \times \frac{35 \text{ yrs}}{70 \text{ yrs}} \times \frac{1 \text{ yr}}{365 \text{ days}} = 4 \times 10^{-7} \text{ mg/kg/d}$$

2. Home Lawns = 4×10^{-7} mg/kg/day

$$2.7 \times 10^{-5} \text{ mg/kg/yr} \times \frac{35 \text{ yrs}}{70 \text{ yrs}} \times \frac{1 \text{ yr}}{365 \text{ days}} = 4 \times 10^{-8} \text{ mg/kg/d}$$

The oncogenic risks of cadmium were calculated by multiplying the cancer potency of 6.1 $(\text{mg/kg/day})^{-1}$ times the LADD:

1. Golf courses

   a. Hand held spray gun

      Summer = 1×10^{-4}

      $6.1\ (\text{mg/kg/day})^{-1} \times 2 \times 10^{-5}$ mg/kg/day = 1×10^{-4}

      Late fall/winter = 2×10^{-4}

      $6.1\ (\text{mg/kg/day})^{-1} \times 4 \times 10^{-5}$ mg/kg/day = 2×10^{-4}

   b. Mixer/loader = 1×10^{-6}

      $6.1\ (\text{mg/kg/day})^{-1} \times 2 \times 10^{-7}$ mg/kg/day = 1×10^{-6}

   c. Ground Boom = 2×10^{-6}

      $6.1\ (\text{mg/kg/day})^{-1} \times 4 \times 10^{-7}$ mg/kg/day = 2×10^{-6}

2. Home owner = 2×10^{-6}

   $6.1\ (\text{mg/kg/day})^{-1} \times 4 \times 10^{-8}$ mg/kg/day = 2×10^{-8}

D. EFFECT RATIOS FOR KIDNEY EFFECTS

Because of the demonstrated effect of cadmium on the kidney as described in section II.A.4, the Agency has conducted a quantitative assessment of the comparison of the demonstrated lowest observable effect level (LOEL) for kidney effects to the estimated exposures from the registered uses. These comparisons are expressed as "Effect Ratios " (ERs) which are the LOEL divided by the estimated exposures (LOEL/estimated exposure).

Friberg et al. (1974) estimated that the value (LOEL) of 5 ug/kg/d is associated with renal dysfunction in humans. The Agency recognizes that this is a chronic dose; however, it is appropriate to use because (1) cadmium is a cumulative toxicant (an acute exposure will add to the body burden) and (2) the half-life of cadmium in the body is lengthy. Animal studies show that excretion via urine and the gastrointestinal tract is extremely low and only to a minor degree related to total body burden (Friberg, et al., 1971).

The 1974 Friberg et al. study resulted in a LOEL of 2 ug/m^3 or 2 x 10^{-6} ml/L. Assuming a 70 kg applicator with a respiratory rate of 12 L/min and a daily exposure throughout the year, the annualized LOEL via inhalation is 0.18 mg/kg/yr. To make the quantitative assessment or effect ratio, the Agency divided this annualized LOEL by the inhalation exposure estimates for each application scenario.

However, to calculate the ERs from dermal exposure an adjustment to the annualized LOEL is necessary to account for the differences in exposure routes: inhalation in the experimental model to derive the LOEL and dermal exposure from cadmium application. This adjustment is accomplished by multiplying

the annualized LOEL by the ratio of absorption rates for inhalation (40%) to dermal (1%) exposure (Friberg, 1971) to give 7.2 mg/kg/yr. This value was divided by dermal exposure values to give ERs for kidney effects from dermal exposure.

The ERs for the inhalation and dermal exposures for each application scenario are presented in the following table:

Exposure Scenario	Effect Ratios for Kidney
Golf Course Applicator	
Hand spray gun	
Dermal	0.1
Inhalation	4.3
Ground boom	
Dermal	45
Inhalation	418
Combined Applications	
Dermal	0.1
Inhalation	4.0
Home Lawn Applicator	
Dermal	81
Inhalation	6666

These calculations suggest that there are comparatively small ERs for kidney effects for most of the exposure scenarios of the golf-course use patterns and for the home lawn use pattern (dermal). As outlined in the Exposure Assessment (section B of this chapter) the use of chemical resistant gloves (during hand held spray application) and half-face respirators during golf course application would alter these calculations by 10-fold increase for dermal and 10-fold for inhalation. The ERs for home lawn applications do not change because gloves and respirators are not considered practical for home owners.

III. BENEFITS

Approximately 30,000 pounds of cadmium active ingredient are used as turf fungicides annually. Nearly all of the use is on golf courses. The turf diseases controlled by cadmium include copper spot, red thread, and gray snow mold.

Cadmium fungicides are applied to less than 4% of the estimated 13,000 golf courses in the U.S. The National Survey of Pesticide Usage on Golf Courses in the U.S. (April, 1985) indicates that cadmium was used on golf courses with a combined total area of approximately 50,000 acres. Cadmium use was mostly on the greens and tee areas of these courses (which comprise only about 5% of the total golf course acreage). Cadmium applications were concentrated in the region consisting of Minnesota, Wisconsin, Illinois, Indiana, Ohio and Michigan.

Although several fungicides are available to control the copper spot, red thread, and gray snow mold turf diseases, only cadmium and triadimefon are registered to control all three diseases. Other fungicides which are registered to control one or more of these diseases include: thiram, thiophanate-methyl, thiophanate-ethyl, PCNB, mancozeb, fenarimol, chlorothalonil, chloroneb, captan, and anilazine.

Because triadimefon is the only fungicide which is registered to control each of the turf diseases controlled by cadmium, it was assumed that all golf course acreage historically treated with cadmium would be treated with triadimefon if cadmium were unavailable. Based on this assumption, the economic impact

of the cancellation of cadmium fungicides is estimated to be $240,000 annually. The increased cost of substituting triadimefon would be approximately $500 annually for each of the affected golf courses. This estimate may overstate the economic impact of cancellation since other fungicides less expensive than triadimefon could be substituted for cadmium for some of the turf diseases. Data were not available to determine the extent of cadmium use for each of the three separate turf diseases to more accurately assess the costs of a cadmium cancellation.

IV. RISKS FROM ALTERNATIVES TO CADMIUM

The pesticide alternatives to cadmium compounds are listed in section III. (Benefits) of this document. The Agency has information on the oncogenicity, mutagenicity, reproductive and teratogenicity/fetoxicity effects for many of these alternatives. Table IV-1 summarizes these effects. For many of the chemicals their data base is incomplete, especially for anilizine and thiram. Without a complete data base, it is not possible to fully judge the relative toxicities of the alternatives as compared to cadmium. These data will be obtained through the Agency's Registration Standard program.

As indicated in Table IV-1, the Agency has initiated or completed Special Reviews and/or Registration Standards on a number of the alternative fungicides. Registration Standards will follow for the others in the future. As a result of these reviews, the Agency has made regulatory decisions on a number of fungicides. In cases where there were potential unreasonable adverse effects, the Agency took actions to reduce risks; where data were invalid or lacking, the Agency has required additional data pursuant to FIFRA 3(c)(2)(B). As these data are received and evaluated, the Agency will be better able to make regulatory decisions on each of the fungicides.

Table IV-1 : SUMMARY OF TOXICOLOGICAL EFFECTS OF CADMIUM ALTERNATIVES

Alternative	Onco	Muta	Repro	Terata	Regulatory Status
Anilazine	?	?	?	?	RS completed 12/83
Captan	+	+	-	+	SR in progress
Chloroneb	-	-	-	-	RS completed 9/80
Chlorothalonil	+	-	-	-	RS completed 1/81
*Fenarimol	+	-	+	+	
Mancozeb	1	+	+	+	SR completed 10/82 RS scheduled 1987
PCNB	+	-	-	?	SR completed 4/82
Thiophanate-methyl	-	-	-	-	SR completed 10/79 RS completed 5/86
Thiophanate-ethyl	-	?	N/A	-	RS completed 12/85
Thiram	?	?	?	?	RS completed 7/84
*Triadimefon	-	-	-	+	

+ = positive effects
- = no effects
? = data gap or not known at this time
SR = Special Review
RS = Registration Standard
1 = oncogenic risk assessment in progress
N/A = not applicable due to lack of appropriate exposure
* = first registered after 1977

For many of the alternatives there are complete data bases. Chloroneb and thiophanate-methyl have not been shown to be positive for any of the above toxicological parameters. Thiophanate-methyl was Special Reviewed on the presumption of mutagenicity which was successfully rebutted. Captan is positive for oncogencity, mutagenicity and teratogenic effects; it is for these reasons that captan is undergoing a Special

Review; cancellation of all uses has been proposed pending receipt of residue data necessary to finalize dietary risk estimates. Chlorothalonil may have oncogenic potential based on a mouse study which lacked a dose-related response; an additional study in the rat has been required. Fenarimol has been demonstrated to be positive for oncogenicity, reproductive and teratogenic effects. However, the oncogenic risk is less than 10^{-6}; the teratogenic MOS is greater than 700; and, the reproductive effects shown in laboratory animals has been determined to be inapplicable to humans. Mancozeb, one of the EBDC compounds, metabolizes to ETU which is a suspected oncogen. Additional oncogenic related data have been generated by EBDC registrants and are being assessed by the Agency. PCNB (pentachloronitrobenzene) was special reviewed because of oncogenic potential from a manufacturing contaminant (hexachlorobenzene). The Special Review was terminated because the manufacturers have revised the manufacturing process to reduce the contaminant concentration to an acceptable level. Triadimefon has been shown to produce teratogenic effects; however, there are comparatively large (>100) MOSs.

V. PROPOSED REGULATORY ACTIONS

A. INTRODUCTION

FIFRA requires the Agency to weigh the risks against the benefits for each use of a pesticide in order to determine whether continued registration would cause unreasonable adverse effects on the environment. In Chapters II and III, the risks posed by exposure to cadmium fungicides and the benefits derived from their registered uses were discussed. Chapter IV described the risks associated with alternative pesticides.

Finally, this section identifies the regulatory options available to the Agency to reduce the risks from the registered uses of cadmium fungicides. Three options have been identified and evaluated for their impact on the risks and benefits of the registered uses and the most appropriate regulatory option has been proposed.

B. RISK CONCLUSIONS

Exposure to cadmium fungicides can occur through application to turf of golf courses and home lawns. Exposure to other forms of cadmium can also occur in industrial work areas, drinking water and other environmental substrates. From these sources, the entire U.S. population is likely to be exposed to cadmium from pesticide and/or nonpesticide uses and sources. These exposures and associated risks were discussed in detail in sections I.B. and II.B., C. and D.

1. Oncogenicity

Based on the results of studies in which (1) rats exposed to cadmium chloride aerosol by inhalation developed lung tumors, (2) rats and mice injected with cadmium or cadmium salts developed injection site, testicular and pancreatic islet tumors, (3) rats and mice orally administered cadmium did not develop significant increases in tumors and (4) workers exposed to airborne cadmium and cadmium compounds experienced a dose-related increase in lung tumors, the Agency classified cadmium as a Group B1 substance or a "probable" human carcinogen (Proposed Guidelines for Carcinogenic Risk Assessment, 1984).

The Agency calculated a cancer potency (Q_1^*) of 1.8×10^{-3} $(ug/m^3)^{-1}$ or 6.3 $(mg/kg/day)^{-1}$ based on a linear model and the observed incidences of lung cancer from smelter workers (Thun et al., 1985) which was discussed in section II.A.1. This potency along with the estimates of exposure were then used to estimate the upper limit probabilities of excess oncogenic risks to humans involved in the application of cadmium fungicides. The specific risks for oncogenicity are presented in section II.C.

2. Kidney Effects

Animal and human studies have demonstrated the relationship of cadmium exposure to acute and chronic kidney effects (section II.A.4.). Acute effects are fatty body formation and renal tubule degeneration; chronic effects include renal dysfunction. The Agency calculated estimates of ER's for kidney effects by

using the LOEL of 2 ug/m^3 or 2 x 10^{-6} ml/L from autopsies and biopsies of cadmium factory workers (Friberg, et al., 1974) and the estimated application exposures (section II.B.4.). The ER's range from 0.1 (dermal) and 4.0 (inhalation) for combined golf course applications to 81 (dermal) and 6666 (inhalation) for home lawn applications. Based on the results of animal and human studies and the low ERs, the Agency has concluded that the risk criterion at 40 CFR 154.7(a)(2) has been met.

3. Mutagenicity

As previously discussed in section II.A.2. cadmium compounds have been used in a variety of mutagenicity studies. In gene mutation studies, results were inconclusive in micro-organisms and only marginally positive in mammalian cell cultures. Results were conflicting in chromosomal aberration studies with human lymphocytes from exposed factory workers. In vivo chromosomal aberration studies with rodent species have provided conflicting results. No dominant lethal mutations or heritable translocations were observed in mouse studies. Evidence suggests that cadmium does interfere with spindle formation in both in vivo and in vitro studies with mammals. However, because of the many end points and protocols that have been used and because of conflicting results, the Agency has concluded that a clear, unequivocal determination of cadmium's mutagenic potential cannot be made.

4. Teratogenicity, Fetotoxicity and Reproduction

The teratogenicity and fetotoxicity triggers in the PD-1 were based on (1) rat, mouse and hamster studies where cadmium was seen to transfer across the placenta directly affecting the fetus as well as inducing maternal toxicity and (2) the Agency's exposure estimates of potential risks to women from home lawn use. A review of the studies, as discussed in section II.A.3., indicated that developmental toxicity (embryotoxicity, fetotoxicity and teratogenicity) of cadmium in experimental animals is mainly dependent upon the dose and route of administration. A rat inhalation study resulted in a NOEL of 0.6 mg/m^3 for developmental effects.

The available data are now considered to be inadequate to fully assess the effects of cadmium on human reproductive function or development. There is limited evidence that human exposure to very high levels of cadmium may induce testicular damage.

C. BENEFIT CONCLUSIONS

The benefits of cadmium fungicides were assessed in terms of economic impact which would result if its uses were cancelled and users were forced to employ available alternatives. As discussed in section III., should cadmium fungicide uses be cancelled, only minimal economic impacts would result for golf courses and practically no impacts would result for home owners since use appears to be inactive. If triadimefon would replace cadmium uses, the additional cost nationwide is estimated to

be approximately $240,000 or $500 for each of the affected golf courses. Although not quantified, other alternatives such as triadimefon are cheaper and/or applied less frequently than cadmium and if used as replacements could offset the above minimal cost increase.

Registered alternatives exist for all uses of cadmium but only triadimefon is registered for all of cadmium's major uses --control of red thread, copper spot and grey snow mold. Each of the other ten alternatives is registered for only one or two of these fungal diseases. Also, cadmium provides the user with another fungicide for rotation with other alternatives to curtail resistance problems.

D. DEVELOPMENT OF REGULATORY OPTIONS

There are three basic options for regulating all pesticides:

Option 1: Continuation of Registration Without Changes

Option 2: Continuation of Registration With Modifications to the Terms and Conditions of Registration

Option 3: Cancellation of Registration

The two extreme Options, 1 and 3, are at the opposite ends of the risk/benefit spectrum. Adoption of Option 1 is appropriate when the Agency has concluded that the level of risk is acceptable in light of the pesticide's benefits and that further risk reduction measures are not necessary to assure that the use of the pesticide meets the statutory standard for continued registration.

Adoption of Option 3, cancellation, is appropriate when the Agency has concluded that the risks from a use outweigh the benefits of that use, and that these risks cannot be mitigated to an acceptable level by any other measures short of cancellation. Cancellation may affect all uses of a compound, only specific uses, or specific application methods.

Option 2 is appropriate when the risks of a pesticide use can be reduced to a level where the benefits of use outweigh the risks. This risk reduction is accomplished by modifying the terms and conditions of the pesticide's registration. These modifications, which are expressed through the pesticide's labeling, are changes in the manner the pesticide is to be used.

These changes are designed to reduce exposure to the pesticide and thereby reduce or eliminate the risk from the pesticide. The following risk reduction measures were considered and evaluated for their potential effectiveness and feasibility.

1. Measures to Reduce Exposure to Mixers, Loaders and Applicators

a. Protective Equipment

Dermal and inhalation exposure to cadmium fungicides can occur during mixing, loading, applying and maintaining application equipment. During these combined activities of golf course application, protective equipment comprised of elbow length, chemically resistant gloves and half face respirators would reduce dermal exposure up to two orders of magnitude, according to the Daniel et al. study, and inhalation exposure up to one order of magnitude, respectively. If implemented,

protective equipment requirements would have minimal impact on economic benefits. However, there is concern for the practicality of imposing respirators for golf course and gloves and respirators for home lawn applicators. There is reason to doubt that there would be high compliance or proper use because of cost, training, and/or inconvenience.

b. Modify Application Methods for Use with Highest Exposure

Cadmium application by hand held spray equipment to golf greens and tee areas results in the highest exposures. Hand held application equipment is used on these areas rather than large, heavy mechanical application equipment, such as ground boom sprayers used on fairways, because of the need to maintain a smooth, consistent, textured playing surface. If the Agency imposed a requirement prohibiting the use of hand held spray equipment, there would be impact to the users due to a lack of suitable alternative application equipment. This would be tantamount to cancellation of this specific use. Similarly, for the home lawn use a prohibition against the use of hand held spray equipment would be tantamount to cancellation.

E. RISK/BENEFIT ANALYSIS OF REGULATORY OPTIONS

If the registrations for cadmium compounds for use on golf courses and home lawn turf were continued without any additional restrictions (Option 1), the total oncogenicity risks would be 10^{-4} to 10^{-6} for golf course applicators and 10^{-8} for home lawn applicators. Also, there would be low ERs for kidney effects for certain golf course application scenarios; the kidney ERs associated with home lawn use are much higher but

are still of concern. The benefits for the uses on golf course, estimated to be approximately $240,000 or $500 for each of the affected golf courses would remain unaffected by continued unrestricted use. Benefits from the use on home lawns would remain negligible.

Also, the Agency is concerned about the purposeful addition of cadmium, a heavy metal, into the environment. Cadmium pesticide products are produced for the intent of direct application to sites in the environment in comparison to cadmium compounds that enter the environment as by-products of industrial production. Given the generally accepted undesirable characteristics of adding heavy metals to the environment and the low benefits from applying cadmium pesticides, the Agency does not believe it prudent to condone the willful addition of cadmium pesticide compounds, especially at a maximum permissible level (13 lbs/A/yr) that is about 30 times the level (0.44 lb/A/yr or 1.25 kg/ha/yr) permitted in land-spreading of sludge containing cadmium.

The Agency has concluded that these risks are unacceptable in light of the small benefits and would be insufficiently mitigated by the use of protective equipment--elbow length, chemically resistant gloves and a half-face respirator (Option 2.) For the golf course use full compliance and proper use of gloves and a respirator, which is questionable, would reduce the oncogenic risks one order of magnitude to 10^{-5} and increase the kidney effect ratios to levels that would still be as low as 10. For the home lawn use, the Agency believes the use of gloves and a respir-

ator are not practical; the oncogenicity risk remains 10^{-8} and the kidney effect ratios remain unchanged at 81 (dermal) and 6666 (inhalation). The Agency concludes that while these risks are low, they nevertheless are unacceptable because of the negligible benefits associated with the home lawn use.

F. SUMMARY OF PROPOSED DECISION

The Agency proposes to cancel all uses of all cadmium fungicide compounds. This proposed decision is based on (1) the toxicological evidence of cadmium's effects on humans and laboratory animals, (2) estimates of cadmium exposure to workers involved in the application of cadmium fungicides, (3) the estimated risks to these workers for developing oncogenic and kidney effects, (4) the inadequacy of additional and reasonable protective measures that would reduce the risks to acceptable levels, (5) the availability of effective alternatives and, (6) the low benefits of use and the minimal economic impact of cancellation.

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